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EXAMINER
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ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/419,545	DARJI ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-23* is/are pending in the application.

4a) Of the above claim(s) *11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,10 and 17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Applicants' Amendment

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 12/13/04 in response to the non-final Office Action mailed 08/11/04. The amendment to the base claim includes deletion of several limitations and the addition of the limitation 'under the control of an eukaryotic promoter'.

Status of Claims

2) Claims 1, 9, 10, 17, 18 and 21-23 have been amended via the amendment 12/13/04.

Claims 1-6 and 9-23 are pending.

Claims 1-6, 9, 10 and 17-23 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

5) The rejection of claim 9 made in paragraph 13(c) of the Office Action mailed 03/29/02 and maintained in paragraph 24 of the Office Action mailed 12/10/02, paragraph 14 of the Office Action mailed 08/13/03 and paragraph 24 of the Office Action mailed 08/11/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

6) The rejection of claim 1 and those dependent therefrom made in paragraph 25 of the Office Action mailed 08/11/04 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to claim 1.

7) The rejection of claim 1 and those dependent therefrom made in paragraph 27 of the

Office Action mailed 08/11/04 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to claim 1.

8) The rejection of claim 1 made in paragraph 28(a) of the Office Action mailed 08/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

9) The rejection of claim 1 made in paragraph 28(b) of the Office Action mailed 08/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claims 9 and 23 made in paragraph 28(c) of the Office Action mailed 08/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

11) The rejection of claim 10 made in paragraph 28(d) of the Office Action mailed 08/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

12) The rejection of claim 23 made in paragraph 28(e) of the Office Action mailed 08/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claims 2-7, 9, 10 and 17-23 made in paragraph 28(f) of the Office Action mailed 08/11/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants amendment to the base claim.

14) The rejection of claims 1, 2, 10 and 18-20 made in paragraph 29 of the Office Action mailed 08/11/04 under 35 U.S.C. § 102(b) as being anticipated by Yang *et al.* (*J. Immunol.* 145: 2281-2285, 1990), is withdrawn in light of Applicants' amendment to the base claim(s).

15) The rejection of claims 1, 2 and 18-22 made in paragraph 30 of the Office Action mailed 08/11/04 under 35 U.S.C § 102(b) as being anticipated by Tite *et al.* (*Immunology* 70: 540-546, 1990), is withdrawn in light of Applicants' amendment to the base claim(s).

16) The rejection of claims 1, 9, 10, 17, 19, 22 and 23 made in paragraph 31 of the Office Action mailed 08/11/04 under 35 U.S.C § 102(b) as being anticipated by Verma *et al.* (*Vaccine*

13: 142-150, 1996), is withdrawn in light of Applicants' amendment to the base claim(s).

17) The rejection of claims 1-3, 10, 19 and 20 made in paragraph 32 of the Office Action mailed 08/11/04 under 35 U.S.C § 102(b) as being anticipated by Fouts *et al.* (*Vaccine* 13: 1697-1705, 1995), is withdrawn in light of Applicants' amendment to the base claim(s).

18) The rejection of claims 1, 4 and 5 made in paragraph 33 of the Office Action mailed 08/11/04 under 35 U.S.C § 103(a) as being unpatentable over Tite *et al.* (*Immunology* 70: 540-546, 1990) or Verma *et al.* (*Vaccine* 13: 142-150, 1996) or Yang *et al.* (*J. Immunol.* 145: 2281-2285, 1990) or Fouts *et al.* (*Vaccine* 13: 1697-1705, 1995) in view of Rock (US 5,869,057, already of record) or Sztein *et al.* (*J. Immunol.* 155: 3987-3993, 1995), is withdrawn in light of Applicants, amendments to the base claim(s).

19) The rejection of claim 6 made in paragraph 34 of the Office Action mailed 08/11/04 under 35 U.S.C § 103(a) as being unpatentable over Tite *et al.* (*Immunology* 70: 540-546, 1990) or Verma *et al.* (*Vaccine* 13: 142-150, 1996) or Yang *et al.* (*J. Immunol.* 145: 2281-2285, 1990) or Fouts *et al.* (*Vaccine* 13: 1697-1705, 1995) as modified by Rock (US 5,869,057, already of record) or Sztein *et al.* (*J. Immunol.* 155: 3987-3993, 1995) as applied to claim 1 above, and further in view of Vogelstein *et al.* (US 6,054,570, already of record), Chada *et al.* (US 5,736,388, already of record), or Frankel *et al.* (US 6,099,848, filed 11/18/1997), is withdrawn in light of Applicants, amendments to the base claim(s).

Rejection(s) Maintained

20) The rejection of claim 18 made in paragraph 26 of the Office Action mailed 08/11/04 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is maintained for reasons et forth therein and herebelow.

Claim 21, as amended now, depends from claim 18 and therefore is added to this rejection.

Applicants contend that the Office position that the specification only supports the recitation 'and/, but not 'or' in claim 18 is unsupported. Applicants state that the description of the various antibody responses occurs in completely separate sentences at page 7. Applicants submit that at lines 15-28 of page 13, the IgG1 and IgG2 responses are discussed independently

of each other without discussion of the IgA response. Applicants conclude that the specification conveys to one of ordinary skill in the art that the specific types of antibody responses are contemplated individually in the alternative.

Applicants' arguments have been carefully considered, but are not persuasive. The specification at lines 17-24 on page 7 of the specification is supportive of the induction of IgG2a, IgG1 **and** IgA antibodies by the *Salmonella typhimurium* strain carrying the eukaryotic expression vector encoding the heterologous antigen, but does not support the induction of IgG2a or IgG1 or IgA antibodies. The last sentence of this passage in the specification states as follows:

> In addition, IgA antibodies were evoked by this immunization schedule (not shown).

The description at lines 15-28 of page 13 of the instant specification represents the work of Mosmann and Coffman, 1989; Sher and Coffman, 1992; Tian *et al*, 1996 as set forth therein, and is unrelated to the outcome of the instant invention. The rejection stands.

New Rejection(s)

The following new rejection(s) are made in this Office. These new rejections are necessitated by Applicants' amendments to the claim(s) previously not presented.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

21) Claims 1-6, 9, 10 and 17-23 are rejected under 35 U.S.C. § 112, first paragraph, as based on a disclosure which is not enabling. The subject matter critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

In the instant application, via the first paragraph on page 8 of their amendment/response filed 12/13/04, Applicants submit that the present application shows for the first time the successful 'genetic immunization' of vertebrates using an attenuated *Salmonella* strain comprising a eukaryotic expression vector. Applicants assert that the invention is not to elicit an antibody response to a protein expressed by the *Salmonella*, rather is 'genetic immunization' using genes or gene fragments that are 'expressed by the host receiving the vaccine'. Applicants state that the vector used in the vaccine harbors a eukaryotic promoter (CMV immediate early promoter) that allows expression of the gene in a eukaryotic host cell. On page 9 of the instant

specification, Applicants assert that the ability of the immunized eukaryotic host to express the gene is an important point because that is the mechanism by which the genetic immunization occurs. Applicants further state that the immune response generated by the vaccine was due to the *in vivo* transfer of the gene and expression of the gene by the mice, not due to the expression of the gene by the *Salmonella*. However, the instant claims, particularly the base claim as currently presented, does not include this subject matter that is asserted to be critical or essential to the invention.

Furthermore, claim 1 has now been amended to delete several limitations and to add the limitation 'under the control of an eukaryotic promoter'. The claim now recites that the attenuated *Salmonella* strain comprises a eukaryotic expression vector 'for the expression of a heterologous gene ..... under the control of an eukaryotic promoter'. The limitations: 'for the expression of a heterologous gene ..... under the control of an eukaryotic promoter' and 'for a vaccination of vertebrates' merely represent the intended use of the strain. Nothing in the claim(s) currently conveys that: (a) the strain or the expression vector comprises a gene as recited and a eukaryotic promoter; (b) a eukaryotic host on genetic immunization with the strain expresses the gene; and (c) the immune response generated by a vaccine comprising the strain is due to the *in vivo* transfer of the gene and expression of the gene by the eukaryotic host. The claimed attenuated *Salmonella* strain comprising a eukaryotic expression vector is not recited as a strain that allows a eukaryotic host to efficiently express the heterologous gene once the eukaryotic host is subject to genetic immunization with the *Salmonella* strain. Additionally, except for claims 17, 18, 21 and 22, claims do not require the induction of a T cell and antibody immune response in the vertebrate host immunized with the vaccine comprising the strain. The claims lack elements critical or essential to the practice of the invention.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

22) Claims 1-6, 9, 10 and 17-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 9 is vague, confusing and/or redundant in the recitation: 'a gene (hly gene)' and 'a gene (actA gene)'. For the purpose of distinctly claiming the subject matter, it is

suggested that Applicants replace the limitations with --a *hly* gene-- and --an *actA* gene-- respectively.

(b) Claim 1 is vague and indefinite in the limitation 'fragment', because it is unclear what is encompassed in this limitation. What constitutes a 'fragment', and how much of the gene's original structure has to be retained such that the resulting product can be considered a 'fragment', is not clear. The metes and bounds of the structure encompassed in the limitation 'fragment' are indeterminate.

(c) Claim 23 is confusing, redundant and/or incorrect in the limitation: 'a gene (hly gene) encoding a non-hemolytic truncated *Listeria monocytogenes*-literiolysin gene (hly gene)'.

(d) Claims 2-6, 9, 10 and 17-23, which depend directly or indirectly from claim 1, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 103

23) Claims 1, 2, 4-6, 9, 10 and 18-20 are rejected under 35 U.S.C § 103(a) as being anticipated by Branstrom *et al.* (US 5,824,538, filed 09/06/1995) in view of Stocker *et al.* (*Intern. Rev. Immunol.* 11: 167-178, 1994).

The reference of Branstrom *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

It is noted that the only structural requirement of the attenuated *Salmonella* strain claimed in claim 1 is that it comprises a eukaryotic expression vector for the purpose of expressing the recited gene under the control of a eukaryotic promoter and that it is suitable for vaccination of vertebrates.

Branstrom *et al.* disclosed an attenuated *Shigella* strain comprising an expression plasmid vector for delivering a mammalian expression plasmid into a mammalian cell (see claims). The attenuated strain expresses a heterologous or homologous antigen(s) inside the mammalian cells of a host to whom it is administered orally as a DNA vaccine. The attenuated strain induces in an individual to whom it is administered an immune response against the heterologous foreign antigen and therefore serves as a vaccine or delivery vehicle for heterologous antigens or DNA (see columns 3, 4, 9 and 10). The strain can express a non-heterologous antigen and serve as a

vaccine for the prevention and therapy of autoimmune disorders (see columns 3 and 4). The strain contains the eukaryotic expression vector, pCMV beta, expressing the *E. coli* beta-galactosidase heterologous antigen under the control of the immediate early promoter from the human CMV (see Example 2). The attenuated strain provided protection against infection by *Shigella in vivo* (see Example 6) and induced B cell and T cell immune responses (see Example 7) and IgA and IgG antibody production and stimulation of Th1 or Th2 help (see lines 53-59 in column 7; and second paragraph in column 20).

Branstrom *et al.* do not teach the delivery vehicle or the carrier strain to be an attenuated *Salmonella* strain.

However, the use of a *Salmonella* strain, such, *S. typhi* or *S. typhimurium* as a live vaccine strain for expressing foreign proteins in vertebrates was well known and routinely practiced in the art at the time of the invention. For instance, Stocker *et al.* identified *S. typhi* Ty21a or *S. typhimurium* as live oral vaccine strains that are available, already in widespread use, proven safe and reasonably effective strains for expression of a heterologous protein (see page 167).

It would have been *prima facie* obvious to one of ordinary in the art at the time the invention was made to replace Branstrom's attenuated *Shigella* strain with Stocker's *S. typhi* Ty21a or *S. typhimurium* vaccine strain to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of producing a vaccine strain for expression of a heterologous gene which strain has already been in widespread use and which has already been proven safe and reasonably effective as a oral-route live vaccine as taught by Stocker *et al.*

Claims 1, 2, 4-6, 9, 10 and 18-20 are *prima facie* obvious over the prior art of record.

24) Claim 3 is rejected under 35 U.S.C § 103(a) as being anticipated by Branstrom *et al.* (US 5,824,538, filed 09/06/1995) as modified by Stocker *et al.* (*Intern. Rev. Immunol.* 11: 167-178, 1994) as applied to claims 2 and 1 above, and further in view of Fouts *et al.* (*Vaccine* 13: 1697-1705, 1995, already of record).

The teachings of Branstrom *et al.* as modified by Stocker *et al.* are described above, which do not expressly disclose the *S. typhimurium* strain to be SL7207.

However, the attenuated *aroA S. typhimurium* SL7207 vaccine strain was known and available in the art at the time of the invention. For instance, Fouts *et al.* taught the attenuated *aroA S. typhimurium* SL7207 vaccine strain specifically for expressing a heterologous antigen to elicit a heterologous antigen-specific immune response in a vertebrate (see abstract; Figure 5; and pages 1698, 1700, 1702, and page 1703, right column).

It would have been *prima facie* obvious to one of ordinary in the art at the time the invention was made to replace the generic *S. typhimurium* vaccine strain in Branstrom's vaccine as modified by Stocker with Fouts' attenuated *aroA S. typhimurium* SL7207 vaccine strain to produce the instant invention with a reasonable expectation of success. Replacement of one art known *S. typhimurium* vaccine strain with another alternative, art known attenuated *S. typhimurium* vaccine strain such as Fouts' SL7207 for the same purpose of expressing a heterologous antigen was well within the realm of routine experimentation, would have been obvious to one of ordinary skill in the art, and would have produced similar results or effects absent evidence to the contrary.

Claim 3 is *prima facie* obvious over the prior art of record.

Remarks

25) Claims 1-6, 9, 10 and 17-23 stand rejected.

It is noted that the limitation '*Salmonella*' in the dependent claim 20 is improperly broadening in scope, because the one recited in the base claim is --the attenuated *Salmonella* strain--.

26) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

27) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (571) 273-8300.

28) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

29) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

S. DEVI, PH.D.
PRIMARY EXAMINER

March, 2005